Epidemiological Section.

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Dr. NEWSHOLME, President of the Section, in the Chair.

Mendelism in Relation to Disease.

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IT was with some trepidation that I accepted an invitation to read a paper bearing upon the inheritance of disease before a distinguished body like the Royal Society of Medicine; but I recollected the motto cut upon the wall of the medical schools at Cambridge—ἀριστος ἰατρος και φιλοσοφος—and I ventured to hope that, even if the remarks which I have to offer to-night might fail to excite the interest of the physician, they would, at any rate, claim the indulgence of the philosopher.

Since the rediscovery of Mendel's paper a few years ago, the experimental study of heredity has made rapid progress, and the recent work has served to confirm and extend the principles which he laid down. What these principles are may be most readily gathered from the consideration of a concrete example, and as a simple illustration we may take a well-known case among poultry, that of the Blue Andalusian fowl. It is a bird which has long been known to possess an inconvenient peculiarity: it will not breed true. It always throws "wasters" of two sorts: blacks, and whites marked with some black splashes. There are, therefore, three kinds of Andalusians, and consequently six possible types of mating among these three varieties. With regard to the results of these types of mating, careful experiment has brought out the following facts:—

Blue	×	Blue	gives	Blacks, Blues, and Whites, in the ratio 1 : 2 : 1.
Blue	×	Black	,,	Blacks and Blues in equal numbers.
Blue	×	White	,,	Blues and Whites in equal numbers.
Black	×	Black	,,	Blacks only.
White	×	White	,,	Whites only.
Black	×	White	,,	Blues only.

We are dealing here with a case in which every possible form of mating has been carried out, and some of the results at first sight seem paradoxical. Thus, for instance, the blacks always breed true whatever their ancestry may have been; and the same holds good for the whites. The white that is produced by two blues, themselves the product of mating blue with blue over many generations, breeds as true to whiteness as the white of pure white ancestry. A black is pure for blackness and a white is pure for whiteness whatever the ancestry of the bird may have been. Again, it seems at first sight incongruous that the mating of black with white should give just twice as many blues as two blues mated together.

The theory of heredity first propounded by Gregor Mendel enables us to summarise all these results in a very simple and beautiful way. Briefly it is as follows. We are dealing with an alternative pair of characters, blackness and whiteness. Every germ-cell or gamete, whether ovum or spermatozoön, bears a representative of this pair. But it can bear only one representative, viz., *either* blackness *or* whiteness. Hence for this pair of characters there are two, and only two, types of gamete: "black" gametes and "white" gametes. When a black gamete meets a black the result is a black bird; when a white meets a white the result is a white bird. But when a white meets a black the resulting zygote contains the representatives or factors for both blackness and whiteness, and develops into a blue bird. Now we must suppose that the gametic representative of a character, the factor, is an unsplittable entity so far as inheritance is concerned. The zygote being formed by two gametes must contain two factors. It is a double structure, and when it comes to form gametes these single structures are produced by the separation of the two factors present in any zygotic cell. The factors representing the characters are said to *segregate* from one another in the process. In a zygote produced by the union of similar gametes, the segregation is between like factors, and all the gametes produced are alike. But a zygote which has been formed by two dissimilar gametes, each bearing one of the factors corresponding to a pair of characters, must on forming gametes give rise to gametes of two sorts, and must give rise to them in equal numbers. On this simple hypothesis is afforded a ready explanation of the various experimental facts given above. A blue hen is producing equal numbers of "black" and "white" eggs—let us say $2n$ of each. To fertilise these eggs are brought large numbers of spermatozoa of the two sorts, black and white, in equal numbers. Every black egg, then,

has an equal chance of being fertilised by a black or a white spermatozoön. In the former case it will form a black and in the latter a blue bird. From our $2n$ black eggs we shall obtain n black and n blue birds. Similarly from our $2n$ white eggs we shall get n blue and n white birds. That is to say, the mating of blue with blue must, on the assumption of the purity of the gametes, give black, blue, and white birds in the ratio 1 : 2 : 1.

Let us now put in a more general form what we have learned from this and similar cases. The characters of plants and animals may in many cases be regarded as existing in alternative pairs. Corresponding to each member of such a pair is something representing it which may

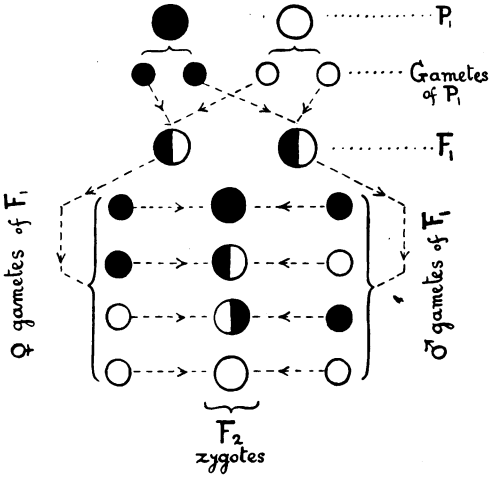


FIG. 1.

Scheme to illustrate inheritance in a simple Mendelian case, such as that of the Andalusian fowl. Gametes from each of the pure parents, the black and the splashed white, meet to form the heterozygous blues. When these come to form gametes the elements representing blackness and whiteness in the germ-cells segregate from one another, so that equal numbers of black and of white gametes are formed. The scheme further illustrates how, from a male and female series of such gametes, the resulting generation comes to consist of two homozygous individuals (one for each character of the pair) and two heterozygotes.

be carried by the gamete. These factors which the gamete carries are the channel by which the qualities of the parent are transmitted to the offspring. Every gamete contains one, and only one, of the factors corresponding to a given pair of characters, *i.e.*, is pure for that character. For any given pair of characters, therefore, there can be

two, and only two, classes of gametes: those pure for one member of the pair and those pure for the other member of the pair. But there can be three different kinds of zygote, for each zygote is formed by the union of two gametes; and since two kinds of gamete exist it is obvious that three kinds of union among them are possible. Two gametes, each pure for one member of the alternative pair of characters, may unite; or two gametes, each pure for the other member of the pair, may unite; or thirdly, two unlike gametes may unite. The zygote so formed contains representatives of each member of the pair and is known as a *heterozygote* (hybrid), whereas zygotes containing representatives of but one member of the pair are termed *homozygotes*. Like the homozygotes, the heterozygote produces pure gametes; only it produces equal numbers of the two kinds instead of producing all of one kind. In this lies the explanation of the fact that hybrids mated together produce a definite proportion of the pure forms, which subsequently breed true without ever giving a hint of their mixed ancestry.

Dominant and Recessive.

In the simplest cases, such as those of the Andalusian fowl, we are dealing with but a single pair of characters, in so far as the gametes are concerned, and we are able to distinguish in appearance the birds arising from the three forms of zygote that these gametes can form. But in a large number of cases it is not possible to distinguish the hybrid from one of the parents. Rosecomb bantams exist in two forms, white and black. Each form breeds true, but when the two are crossed the hybrids all resemble the black parent. The zygote which contains a single dose of blackness grows up into a bird which is as black as the pure black containing a double dose of blackness—a point of difference to the Andalusian, where the zygote with only a single dose of blackness develops into the more or less intermediate blue. In cases such as this of the rosecombs we use Mendel's terms, and speak of the character blackness as *dominant* to whiteness, which is said to be *recessive*. When the hybrids (F_1) are mated together they give, as we have already seen in the case of the Andalusians, one of each of the two homozygous forms for every two heterozygotes. But since black is dominant to white the heterozygotes are indistinguishable in appearance from the dominant homozygote, and this, the F_2 generation, consists visibly of three blacks to every white. The whites subsequently breed true, as do also the

homozygous blacks when they are mated together. But if we wish to separate these homozygous blacks from the heterozygous we must devise some test. And the only test we know of at present is the test of breeding. All the gametes of a homozygous black contain the factor for blackness. Consequently, when such a bird is mated with a white all the offspring must be black. But a heterozygous black is giving off equal numbers of " black " and " white " gametes. Hence, when mated with a white it will form equal numbers of zygotes with and without a black factor, *i.e.*, it will produce equal numbers of black and white birds. The test between the pure dominant and the dominant which carries the recessive character lies in crossing each with the recessive. The former produces only dominants, while the latter gives rise to equal numbers of dominants and of recessives. But whether the phenomenon

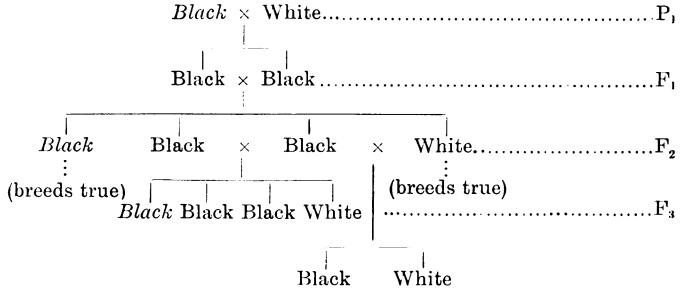


FIG. 2.

Scheme illustrating inheritance in rosecomb bantams. Homozygous blacks in italics to distinguish from heterozygous. P_1 signifies parental generation, F_1 first filial generation, F_2 second filial generation, and so on.

of dominance is present or not, the essential feature of Mendel's discovery is unaffected, and this, of course, consists in the conception of the characters of living things as existing in alternative pairs, and of the purity of the gamete for either member of such a pair.

DIVERSITY OF CHARACTERS SHOWING MENDELIAN INHERITANCE.

Mendel's principles have now been confirmed in many plants and animals, and for many different characters. A few illustrations will serve to give some idea of the diversity of the characters for which these principles have already been shown to hold good. For the sake of convenience they have been arranged under several headings.

Size.—In peas, sweet peas, and many other plants there exist dwarf forms. In the cases hitherto worked out the tall has been shown to be dominant to the dwarf.

Structure.—In plants: the shape of the leaves and of the flowers in primulas, of the seed in *Pisum*, of the flowers and pollen grains in *Lathyrus*, the spines of *Datura*, the beard of wheat, &c. In animals: the long Angora hair of rabbits; in fowls the silky plumage, taillessness, shape of comb, crest, brain hernia, &c.; in mice, hairlessness and the waltzing habit.

Chemical.—Sugary and starchy endosperm in maize; glutenous and starchy endosperm in barley; colour and albinism in animals.

Time of Flowering.—Whether biennial or annual in *Hyoscyamus.*

Colour.—In most plants purple or blue is dominant to red; deeper colours are usually dominant to dilute ones. In animals: grey is dominant to black in rabbits, rats and mice; bay is dominant to chestnut in horses. Black is dominant to brown in the down colour of chickens. Colour differences readily lend themselves to experimental work, and they have been largely made use of in this connection.

Sterility of the anthers in the sweet pea is recessive to the fertile condition. In barley partial sterility is dominant to the completely fertile form.

Immunity to disease in wheat.

From the point of view of medicine the last is probably one of the most important experiments ever made. Mr. Biffen, in Cambridge, crossed a wheat immune to the attacks of yellow rust (*Puccinia glumarum*) with another wheat highly susceptible to such attacks. The hybrids were all severely attacked, and Mr. Biffen experienced some difficulty in saving from them sufficient seed to get a reasonably large crop in the following year. Having grown them on, he found that in this generation came rusted and rust-free plants. Though growing all among and brought into the closest contact with their diseased brethren these rust-free plants showed no sign of contamination. On counting the F_2 generation it was found that out of 2,132 plants, 523, approximately one-quarter, were immune; and such immune plants gave rise to immune offspring only. Susceptibility and resistance to disease in wheat are a pair of characters obeying the Mendelian law of inheritance, and consequently brought completely within the scope of human control.

Human Examples.

And here I may bring forward certain simple cases which concern our own species. Such cases are difficult to come by, for the marriage system of the civilised nations is none too well adapted for the demonstration of Mendelian principles. We have, indeed, but one method, viz., the careful collection of pedigrees and the critical examination of them in the light of the knowledge gained more directly from other species. Among our scanty data a few cases stand out clearly. During the past year Mr. Hurst [1] was able to demonstrate a Mendelian pair of characters in eye colour. Brown pigmentation on the front of the iris is a character dominant to the condition of the iris—whether grey, blue, or violet—in which such brown pigment is absent.

But perhaps the most conspicuous example of Mendelian heredity in man is the case of brachydactyly worked out by Farabee [2] in America, and more recently by Drinkwater [3] in England. This peculiar condition of the hands and feet, which is at the same time associated with shortness of stature, was found by both these authors to be dominant to the normal form. In fig. 3 I have reproduced from his paper the pedigree of Drinkwater's family. In this, as well as in the other human pedigrees with which we shall have to deal, it is always assumed, unless expressly stated to the contrary, that the diseased individual is always mated to a normal. Consequently, in the pedigree, every brachydactylous individual must be regarded as heterozygous and must produce abnormal and normal gametes in equal numbers. Such an individual married to a normal should therefore produce equal numbers of normal and abnormal offspring, just as the heterozygous bantam, mated with a white, produced equal numbers of blacks and whites. Drinkwater found that all the families from abnormal parents together consisted of thirty-nine abnormals and thirty-six normals—a close approximation to the equality which we should expect on Mendelian principles. On these principles, again, we should expect all the normals, being recessive, to breed true, and to give no abnormals when mated with a normal. An inspection of the pedigree shows that this condition is also fulfilled. The evidence, taken with that collected by Farabee, is sufficient to put it beyond all reasonable doubt that we are dealing with a simple Mendelian case, and we may state with confidence that no member of a brachydactylous family who is free from the disease can transmit it to his or her

[1] *Proc. Roy. Soc.*, 1908, Series B., lxxx., p. 85.
[2] "Papers of Peabody," Mus. of Am. Arch. and Ethnol., Harvard Univ., 1905.
[3] *Proc. Roy. Soc. Edin.*, 1908, xxviii., p. 35.

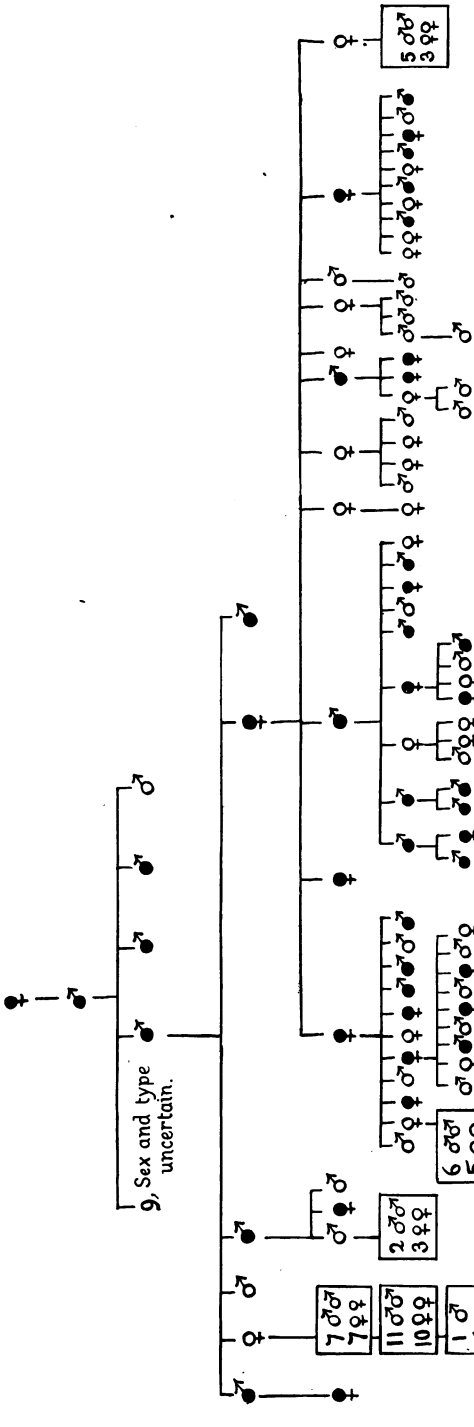


FIG. 3.

Pedigree of a brachydactylous family (from Drinkwater). The affected individuals are shown in black. A few children for whom there was no record as to the brachydactylous condition have been omitted.

offspring; but it can and must be transmitted by the brachydactylous members only.

For one of the most remarkable pedigrees that has ever been got together we are indebted to Mr. Nettleship.[1] It concerns night-blindness, a condition apparently due to loss of the visual purple, and deals with the decendants of one Jean Nougaret, who was born in the year 1637. The pedigree has been brought down to 1907. It extends over ten generations and includes records of more than 2,000 individuals. The diseased condition evidently behaves as a simple dominant over the

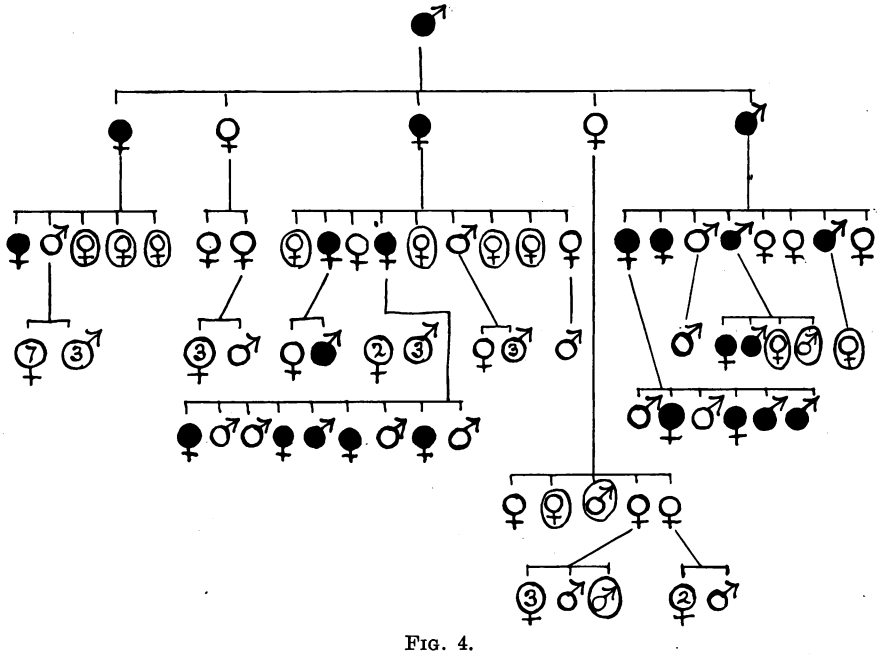


FIG. 4.
Pedigree illustrating the inheritance of diabetes insipidus (polyuria) (after Weil).

normal. During two and a half centuries no normal member of the family who has married another normal, whether a member of the family or not, has ever transmitted the disease. On the other hand, the affected members, who have in almost all cases married normal persons, have transmitted the diseased condition to many of their offspring. The number of diseased is actually somewhat less than half, but, as Mr. Nettleship points out, there is a marked inclination to conceal the disease, which in some cases doubtless has been attended with success. By the

[1] *Opthalm. Soc. Trans.*, 1907, xxvii., p. 269.

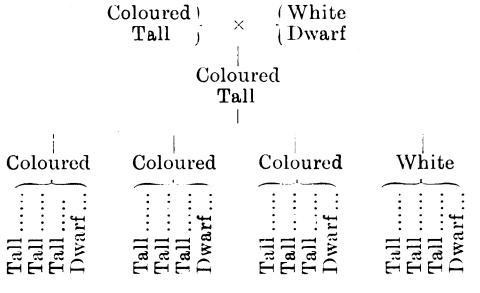
side of a history such as this the other pedigrees which I am able to show you must seem comparatively insignificant. Mr. Bateson has recently been collecting together evidence from various sources on certain forms of hereditary disease. In some of these cases, notably those of keratosis palmæ and congenital cataract, the evidence points to the diseased condition behaving as a simple Mendelian dominant to the normal; and it seems not improbable that other cases, such as diabetes insipidus (fig. 4), irideremia, ectopia lentis, hereditary chorea, and epidermolysis bullosa, may eventually turn out to fall within the same category. In some of them there are records of the disease being transmitted by normals, but whether this is due to mistaken observation or whether it indicates some more complicated scheme of inheritance must be left for future investigation to decide.

So far we have considered only the simplest of cases, involving but a single pair of alternative characters. Nevertheless, we have already been able to analyse successfully cases in which two or more pairs of characters play a part. Though no human examples of this nature are at present known to us with any degree of certainty, there is little doubt but that conditions similar to those I am about to describe will eventually have to be investigated for our own species; and a proper understanding of the principles based upon the hereditary behaviour of the colour of the rabbit and of the sweet pea may well serve in the future to illuminate some of the obscurer phenomena of disease in man.

Dihybridism.

Dihybridism is the term applied to cases in which the parents crossed differ from one another in two pairs of alternative characters. It was found by Mendel that in such cases the inheritance of each pair follows the same rule, but follows it independently. Tallness in the pea is dominant to dwarfness, and colour in the flowers is dominant to white. When, therefore, a tall coloured is crossed with a dwarf white all the offspring are tall plants with coloured flowers. In the next generation talls and dwarfs appear in the ratio 3 : 1, and coloureds and whites also appear in the ratio 3 : 1. Hence each tall plant has three times as many chances of being coloured as of being white. Similarly the dwarf coloureds must be three times as numerous as the dwarf whites. A moment's consideration will serve to show that the simplest expression which covers all these requirements is nine tall coloured, three tall

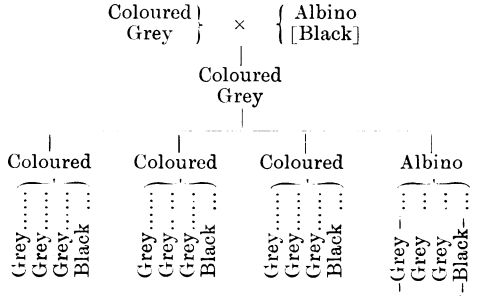
whites, three dwarf coloured, and one dwarf white. And these are the proportions actually found by experiment in this and other cases. This is the 9 : 3 : 3 : 1 ratio characteristic of cases of simple dihybridism, and we may state it in a more general form as follows: When two individuals are crossed which differ in two pairs of alternative characters, the F_2 generation consists of four classes, and, out of every sixteen, nine on the average exhibit both dominants, three one of the dominants and one of the recessives, three the other of the dominants and the other of the recessives, and one exhibits both recessives. The simple and orderly distribution of the characters to form this ratio may be taken as proof that each pair of characters, though obeying the same hereditary law, obeys it independently of the other.



INTERDEPENDENCE OF CHARACTERS.

The distribution of two pairs of characters is not always so simple in appearance as in the case of the peas. The characters belonging to different pairs sometimes interact upon one another, and the way in which this comes about may best be explained by an example. A grey Belgian hare rabbit was crossed with an albino Angora. The progeny were all of the wild grey type. They were in-bred and produced in the next generation greys, blacks and albinos, the proportional numbers of the three kinds being 9 : 3 : 4. The proportion of coloured rabbits to albinos is 3 : 1, suggesting at once that colour and albinism are a pair of alternative characters, of which the former is dominant; and among the coloured the ratio of greys to blacks (9 : 3 3 : 1) points to greyness and blackness forming another pair of characters. If such is the case we ought to find among our sixteen rabbits twelve greys and four blacks. That we only find nine greys and three blacks is because one-quarter of our sixteen rabbits must be albinos, lacking the colour factor which enables the particular colour present, whether grey or black, to declare

itself. There must therefore be both grey albinos and black albinos, and this may be tested by mating an albino with a pure black. Since colour is dominant all the offspring will be coloured, but those albinos which carry the factor for greyness will give greys and those without this factor will give only blacks; and experiment has shown that this is the case. Albino rabbits may be compared to exposed but undeveloped negatives. The silver has undergone a change, but what the image is we cannot say until the developer is poured upon it. So with albino rabbits. By crossing with a black containing the factor which allows the colour to appear, we are, as it were, pouring on the developer, and the resultant colour, whether grey or black, tells us what manner of albino we had to deal with.



The Nature of the Alternative Pair.

At this stage we may ask ourselves a question: What is the nature of these pairs of alternative characters? What is the relation subsisting between the two members of a pair? It is a remarkable fact that we should be able to express all the diverse qualities with which we have been dealing in terms of alternative pairs. Why do we never find longer series of characters—three, four, or even more—which can replace one another as alternatives in the gamete? As the explanation upon which I am about to enter may seem to verge upon the metaphysical, it will be as well to commence it with a concrete illustration. In fowls the rose comb is dominant to the single comb, and these two form an alternative pair. Now, the view of the nature of the rose comb that I wish to suggest to you is that it is a single comb, to which an additional element "roseness" has been added. Singleness underlies roseness, and if our methods were sufficiently delicate to remove this element of roseness from a rose comb we should be left with a single

comb. A rose comb is a single in which an additional element of roseness is present; a single comb is a single because this additional element is absent. And herein lies the explanation of the curious circumstance that the characters of animals and plants can be expressed in terms of

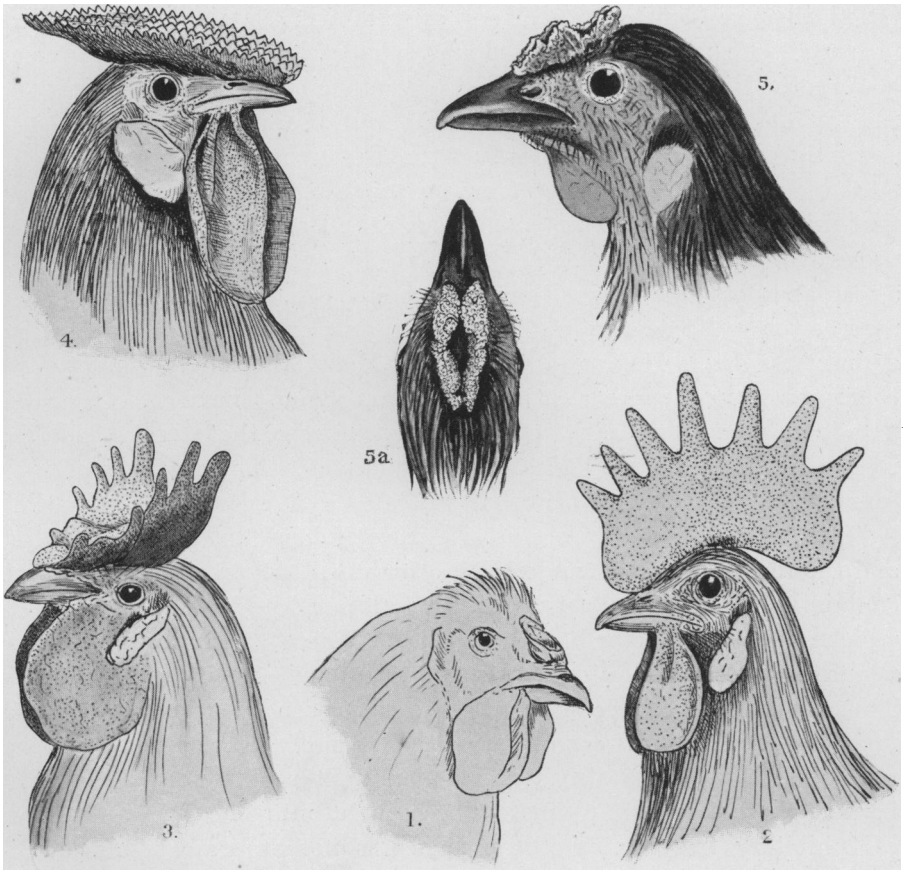


FIG. 5.

To illustrate various forms of comb connected with the Breda × Rose experiments. 1, Breda; 2, Single; 3, Breda × Single; 4, Rose; 5 and 5*a*, Breda × Rose. From two of these last mated together Singles appeared in F_2.

alternative pairs. Such pairs represent the only two relations which the unsplittable factor representing a given character can have with the gamete. It can either be present or it can be absent, and no third

relation is possible. When this view suggested itself to us we at once set to work to devise an experimental test of its validity. We argued that if we could find a fowl with some form of comb recessive to single, and crossed such a bird with a rose-combed bird, we ought to get single-combed birds in F_2. We were fortunate in finding the breed for which we were looking in the Breda fowl, a bird in which the comb is practically non-existent. When crossed with a single these birds produced chickens with large double combs. The combs are duplex because the Breda carries an element of "duplicity" which is dominant to the "simplicity" of the single comb. But the point with which we are immediately concerned is that the Breda cannot carry the factor that makes the single comb, for our crossing experiment has shown that if it did so it would no longer remain a Breda. Having, therefore, proved the absence of single in our Breda, we proceeded to cross it with a rose, and obtained birds with duplex rose combs. These F_1 birds mated together gave Breda combs, duplex and simplex roses, and duplex and simplex *singles*. Having already proved that the single cannot have been present in the Breda, it is obvious that it must have come from the parent rose, and we must consequently suppose that single underlies rose in the way that we have already suggested. The great majority of Mendelian cases fit in with what we call the "presence and absence" hypothesis, and in them we must regard the dominant as the additional and the recessive as the underlying character. All tall peas are dwarfs containing an additional "tall" factor; all purple sweet peas are reds to which a purpling factor has been added. There are, however, cases in which the presence of a quality in the zygote is recessive to its absence. Thus the bearded is recessive to the beardless condition in wheat, and in man the night-blind condition, with its probable absence of visual purple, is, as we have already seen, dominant to the normal. It may be that these cases will ultimately be brought into line by the discovery of inhibitory factors, but the evidence is not at present sufficient to render further discussion profitable.

I have laid some stress upon the presence and absence hypothesis of the relation between the factors of an alternative pair because it is of especial interest in connection with a human disease. The evidence recently collected by Dr. Garrod[1] on alkaptonuria points strongly to this condition being recessive to the normal. With very rare exceptions the alkaptonuric patient is the offspring of normal parents. Such normals

[1] *Lancet*, 1902, ii., p. 1616.

must be regarded as heterozygous dominants, and it is striking to find that the majority of cases involve first-cousin marriages, a condition obviously favourable for bringing heterozygous dominants together. If the diseased condition is recessive, the diseased should form one-quarter of the total number of members of the families in which they occur. Dr. Garrod gives figures for such families. Where the condition of all the offspring has been recorded there are fifty-one normals and sixteen alkaptonurics, a very close approach to the expected ratio of 3 : 1.

The chemistry of the alkaptonuric condition is well known,[1] and the disease depends upon the inability of the organism to bring about a specific reaction by which the benzene ring is broken down and homogentisic acid transformed into lower products. Is the failure of the organism to bring about this reaction due to the absence of a specific intracellular ferment? At present there is little evidence for or against this view, though the work of Czapek and others on homogentisic acid in plants is certainly suggestive. And the fact that the diseased condition is recessive to the normal points to there being something in the normal which is lacking in the diseased. If the chemist could isolate this hypothetical ferment it would serve to clear up our ideas upon the condition known as the diathesis to a disease, and would offer the hope of these conditions falling within the scope of heredity and consequently becoming amenable to human control.

Interaction of Characters.

A beautiful example of the interaction of characters is afforded by the sweet pea. As in most flowers, white is here recessive to colour. All white sweet peas breed true, and in most cases a cross between two whites will result in white-flowered plants only, but when certain strains of whites are crossed together the offspring are all coloured. When a further generation is grown from these plants they produce coloureds and whites in the proportion 9 : 7. The case has now been fully worked out as far as heredity is concerned, and it is evident that we must regard colour as made up of two factors. Each of these factors may be present or absent in a sweet pea, in this way constituting two alternative pairs. We must suppose each of the parent whites of our cross to have been homozygous for the presence of one of these factors and for the absence of the other. If we denote our two factors by C and

[1] *Cf.* Leathes, J. B., "Problems in Animal Metabolism," 1906, p. 195.

R, then the gametes of one white all contained C and not R, while those of the other all contained R and not C. By crossing two such whites a zygote is formed which contains both C and R, the two factors necessary for the production of colour. The gametes of the F_1 plant segregate in the normal way, and as in ordinary cases of dihybridism they give rise to four classes of zygote in the proportion 9 : 3 : 3 : 1. But since only the zygotes containing both dominants can appear different to the rest by showing colour, the three last terms of the ratio, the 3 : 3 : 1 terms, are indistinguishable; hence the ratio 9 : 7. What the symbols C and R represent we do not know. It is tempting to suppose that one of them is a ferment and the other a fermentable substance. Mendelian analysis cannot do more than indicate the presence of these two specific substances. The task of isolation and identification falls within the province of the chemist. Interesting as the case of the sweet pea is from the theoretical side it has also a conceivably practical aspect. In an F_2 family with a 9 : 7 ratio the 7 group consists of five classes of individuals. There are five different kinds of white sweet peas, and in the various types of mating possible between them a cross between two whites may give any of the following results:—

(*a*) All coloured	[CCrr × ccRR][1]
(*b*) Equal numbers of coloured and whites ...	[CCrr × ccRr]
(*c*) One-quarter coloured, three-quarters whites ...	[Ccrr × ccRr]
(*d*) All whites	[Any white × ccrr]

[1] The letters in brackets give a form of mating which would produce the particular result. In most cases the same result may be obtained by several types of mating. For simplicity, however, only one is shown in each case.

And since there are also several kinds of coloured plants (indistinguishable in appearance), the cross between coloured and white may produce any of the following results:—

(*a*) All coloured	[CCRR × any white]
(*b*) Three coloured to one white	[CCRr × ccRr]
(*c*) Equal numbers coloured and white	[CCRr × CCrr]
(*d*) Three whites to one coloured	[CcRr × ccrr]

Lastly, two coloureds crossed together may give either:—

(*a*) All coloured	[CCRR × any coloured]
(*b*) Nine coloured to seven white	[CcRr × CcRr]
(*c*) Three coloured to one white	[CCRr × CCRr]

Now for "coloured" write "diseased," and for "white" write "normal." The number of possibilities is great. Diseased may produce

normals, and normals mated together may produce diseased. True, we know of no such case so far among men, but that is no reason why it should not exist, and it may be that some day the sweet pea will provide the clue to a human disease.

This case of the sweet pea may be paralleled among poultry. We have recently succeeded in finding two white breeds of fowls which breed true to whiteness, which each behave as recessive to colour, but which, on crossing, produce only coloured birds. Moreover, for the following reason, this case of the poultry is even more complicated, for there exist also white fowls whose whiteness is dominant to colour. There are therefore certainly three kinds of white fowls which breed true and may be indistinguishable in appearance, but owe their whiteness to entirely different causes. Fundamental chemical differences are doubtless involved, and the problem may one day be solved by the chemist. At present there is only one method of distinguishing and of separating these similar unlikes, and that is the method of Mendelian analysis.

Gametic Coupling.

In the cases with which we have been dealing, the appearance of a given character depends upon the presence of two factors in the zygote. Yet these factors in heredity behave quite independently, each obeying the simple Mendelian rule. There are, however, cases in which we meet with a new phenomenon, in which there exists a tendency for factors to become definitely associated together or *coupled* in the gamete. Such coupling of distinct characters may be complete. In sweet peas purple is dominant to red, and the erect standard is dominant to the hooded standard; and in families in which purples and reds occur together with erect and hooded standards, the ratio of purples to reds is 3 : 1, and of erect to hooded standards is also 3 : 1. If this were a simple case of dihybridism, such as we have already dealt with in peas, we should expect the distribution of erect and hooded standards among the purples and reds to be governed by the laws of chance, and we should expect our generation to consist of the four classes: erect purple, hooded purple, erect red and hooded red in the normal ratio 9 : 3 : 3 : 1. This, however, is not the case. All the reds display the erect standard and the hoods are all to be found among the purples. Consequently, our family consists of hooded purples, erect purples, and erect reds in the ratio 1 : 2 : 1. We are driven to suppose that all the gametes which

carry hood carry purple also, and that only the red gametes carry the factor for erectness. In other words there is complete coupling in the gamete between purpleness and hood on the one hand, and between redness and erectness on the other. Since every red gamete must carry also the factor for erectness, it follows that in such families as these all the reds must be associated with, and breed true to, the erect character.

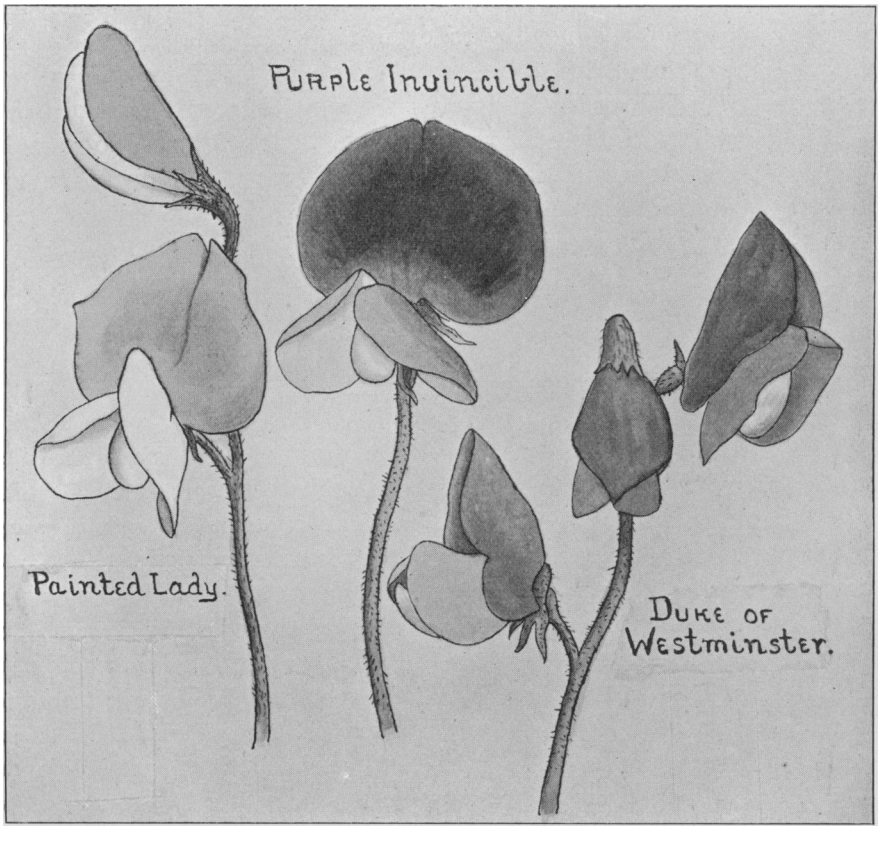


Fig. 6.

Showing three sweet peas: (*a*) red, with erect standard; (*b*) purple, with erect standard; and (*c*) purple, with hooded standard.

Nevertheless we know that hooded reds may occur in other strains. What the conditions are which determine whether hood and redness may or may not be found in the same gamete is a problem which we are experimentally attempting to solve.

Partial Coupling.

Coupling between characters is, however, not always complete. Among sweet peas there are two distinct varieties of pollen grains—elongated or "long," and "round." The long behaves as a simple dominant to the round. In families which contain purples and reds, and also long and round pollens, the ratio of purples to reds is 3 : 1, and the ratio of longs to rounds is also 3 : 1, but there is a marked tendency for long pollen to be associated with the purples and for round pollen to stick to the reds. The coupling is, however, not absolute. The long purples are about twelve times as numerous as the round purples, and this deficiency of rounds is compensated for among the reds, where they are more than three times as numerous as the longs. We must suppose that there is a coupling of purpleness with long and of red with round in most of the gametes, though not in all. If we imagine that out of every eight purple gametes seven carry longness and one carries roundness, and that out of every eight red gametes one carries longness and seven carry roundness, we find that the calculated composition of a generation produced by such a series of ♂ and of ♀ gametes closely accords with the experimental facts. We know of other cases of this partial coupling of characters, though of the processes of cell division by which it is brought about we can at present say nothing. Enough, however, is known to make it certain that it often plays an important part in heredity, and I have laid some stress upon it because it may eventually be found to throw light upon the alleged association of certain physical peculiarities in man with particular forms of disease.

Sex-Limited Diseases.

It is well known that certain diseases are limited almost, if not entirely, to one sex. In hæmophilia, for example, it is, with the rarest exception, the males alone who are affected. But the disease can be and normally is transmitted by the unaffected female, though not all the females of a hæmophilic family are capable of doing so. The affected male is also known to transmit the disease (*cf.* fig. 7). Besides hæmophilia there are certain other diseases which are known to exhibit a somewhat similar mode of transmission—the "Knight's move" in heredity, as Bateson has termed it. Among these may be mentioned colour-blindness, night-blindness when associated with myopia, and

possibly also Gowers's disease. Moreover, the data collected by Herringham on peroneal atrophy seem to suggest that here again we are concerned with a phenomenon of much the same class. In all these cases, where the disease is almost exclusively confined to one sex, it is probably not without significance that the males are the ones to suffer.

Though, as we shall see later, the problem of these sex-limited diseases offers points of special difficulty, the following experiments on sheep suggest the lines along which the solution must probably be sought.

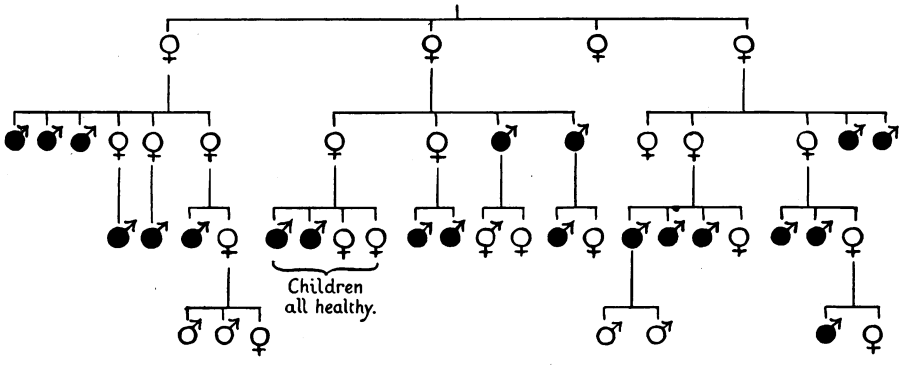


FIG. 7.

Pedigree illustrating the inheritance of hæmophilia (after Stahel).

Professor Wood recently crossed the horned Dorset with the hornless Suffolk breed of sheep. Whichever way the cross was made the ♂ ♂ were all horned and the ♀ ♀ hornless. On breeding together the F_1's all the four types appeared in the offspring, but the horned ♂ ♂ were three times as numerous as the hornless ♂ ♂, while only one out of every four ♀ ♀ was horned. The simplest explanation is to suppose that horns are dominant in the ♂ but recessive in the ♀. This was tested by a pretty experiment, in which an F_2 hornless ♂ was put on to the flock of hornless F_1 ♀ ♀. On the suggested explanation the F_2 ♂ cannot carry the horned character, but the F_1 ♀ ♀ from their breeding must carry this character. The cross must therefore result in equal numbers of animals pure for hornlessness and heterozygous for horns. Now the ♂ ♂ which are heterozygous for the horned character show it, while the ♀ ♀ do not; hence the expected result of our mating is that half the ♂ ♂ will be horned, half will be hornless, and that all the ♀ ♀ will be

without horns. The experiment gave eight horned ♂ ♂, nine hornless ♂ ♂, and eleven hornless ♀ ♀. The visible effect is that the hornless ♀, in contradistinction to the hornless ♂, can transmit the horned character, but only to her ♂ offspring. Again, because the horned character is recessive in the ♀, it follows that every horned ♀ must be pure for that character, and must therefore transmit it to all her offspring. And since every heterozygous ♂ is horned, all the male offspring of any horned ♀ crossed with any ♂ must be horned. This again is in accordance with experiment.

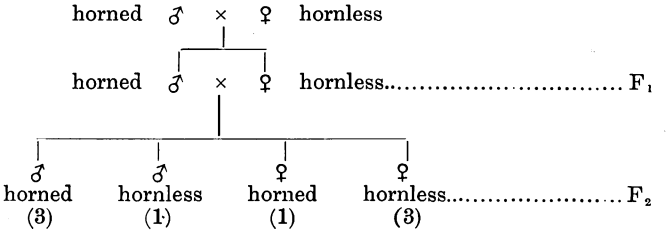


FIG. 8.

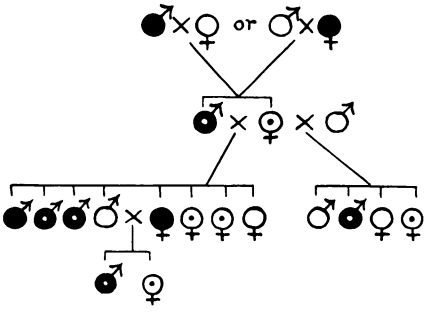


FIG. 9.

Scheme to illustrate the inheritance of horns in sheep. ♂ and ♀ denote males and females homozygous for the horned character; ♂ and ♀ denote males and females homozygous for the hornless character; a heterozygous male is represented by a black circle with a white central dot, and a heterozygous female by a plain circle with a black central dot. Among these the males are horned and the females hornless.

On the assumption that horns are dominant in the ♂ and recessive in the ♀, it follows that there are three kinds of males, viz., those homozygous for the horned character, those homozygous for the hornless character, and those which are heterozygous. Similarly the females are

constitutionally of three kinds. But while the heterozygous males are horned the heterozygous females are hornless. In fig. 10 I have drawn up a scheme to illustrate the nine possible forms of mating between our three females and our three males. One point to notice is that while horned females can only appear when the male parent is horned (Nos. 1, 2, 4, 5), the horned males may also arise from two hornless parents (No. 8). Another important point is that all the male offspring of a horned female must be horned (Nos. 1, 4, 7).

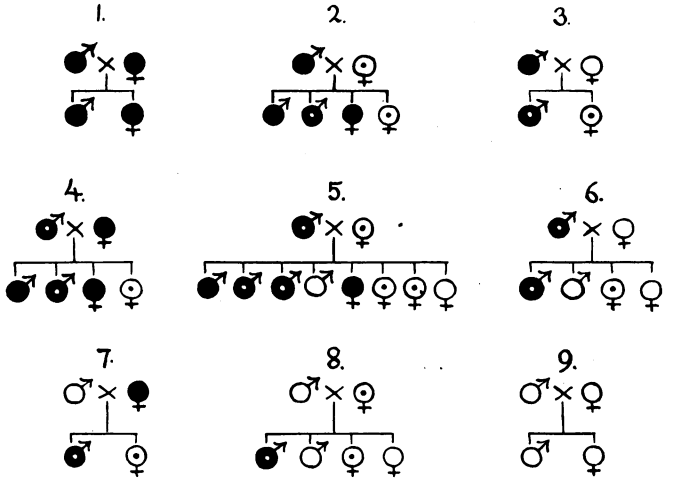


FIG. 10.

Scheme to illustrate the nine types of mating and their results in a case where a character is dominant in one sex and recessive in the other. The character is here represented as dominant in the male and recessive in the female. A heterozygous male is figured as a black circle with a white central dot, and a heterozygous female as a plain circle with a black central dot.

We may now inquire how far this scheme of inheritance fits such cases as those of hæmophilia. A hæmophilic male or a female from a hæmophilic family will almost always marry a normal person outside the family. With the rarest exceptions, therefore, every affected male will be heterozygous in constitution. Consequently the three types of mating with which we are mainly concerned are Nos. 5, 6, and 8. Since a member of an affected family nearly always marries outside of the family, the great bulk of the matings will be of types 6 and 8, and in both of these the male offspring alone are affected. The third type of

mating (No. 5), where an affected male marries a heterozygous female, must be very much rarer than the other two. This type can lead to the production of affected females, but as the chances of such females appearing are only one in four, it must often happen that all the females in these families are normal. The great rarity of female "bleeders" is the natural outcome of the exogamous habits of civilised man.

We have seen that the horned ewe must always transmit the horned character to *all* her male offspring (fig. 9). By analogy we should expect all the sons of a female "bleeder" to be affected. Unfortunately, our data do not allow of this crucial test in the case of hæmophilia, but in the case of colour-blindness there exist a few records of the offspring of colour-blind women mated with normal men. Mr. Bateson tells me that the five such women, about whom he has been able to collect information, had between them twelve sons, *all of whom were colour-blind*, while the daughters, so far as is known, were all normal. It would therefore appear that, qualitatively, the inheritance of these sex-limited diseases is closely comparable to that of horns in sheep.

But Bateson[1] has already pointed out that the proportions in which affected males appear in families of type 8 are far too high. A simple Mendelian interpretation demands equal numbers of affected and unaffected, but, as a matter of fact, the affected males are more than twice as numerous as the unaffected. There is evidently some further complication, possibly some form of coupling between the factors upon which the disease depends and those of sex. That some such form of coupling may exist is rendered probable from the following experiments in animals.

Doncaster and Raynor[2] have recently investigated the inheritance of the pale *lacticolor* variety of the common currant-moth, *Abraxas grossulariata* (fig. 11). The variety behaves as a recessive to the normal form in both sexes, but, as the accompanying scheme shows, there is only one form of mating from which a *lacticolor* ♂ can arise, viz., heterozygous ♂ × *lacticolor* ♀. For when heterozygous individuals are bred together, or when ♂ *lacticolor* is crossed with a heterozygous ♀, the variety only appears in the female offspring. From these results the authors have made some interesting deductions concerning the nature of sex, but for our purpose it is sufficient to call attention to them as illustrating a form of coupling between sex and another character which is somewhat different to any other at present worked out.

[1] *Brain*, 1906, xxix., p. 157.
[2] *Proc. Zool. Soc.*, 1906.

A more complicated case at which Mr. Bateson and I are at present working concerns the inheritance of a peculiar deeply pigmented condition of the skin and connective tissues found in the silky fowl. This breed we crossed with a brown Leghorn, and obtained the following

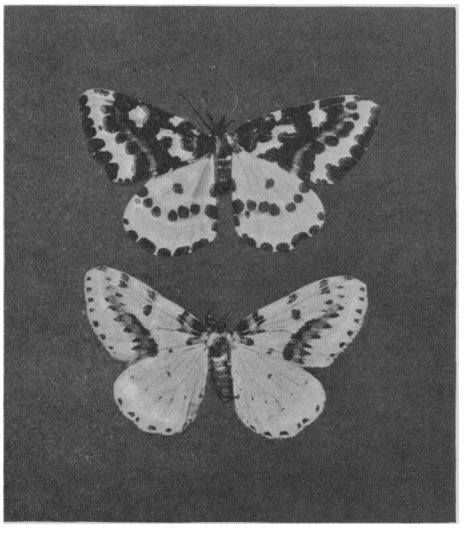


FIG. 11.

The currant-moth, *Abraxas grossulariata*, and its pale *lacticolor* variety.

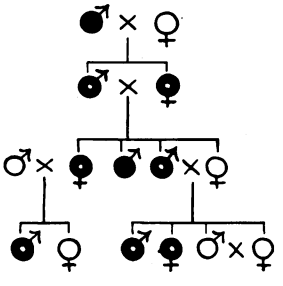


FIG. 12.

Scheme to illustrate the inheritance of the *lacticolor* variety of the currant-moth. Pure *grossulariata* shown black and heterozygotes black with white central dots.

results: From ♀ silky × ♂ brown Leghorn the F_1 birds were practically unpigmented, and such birds bred together gave pigmented and unpigmented birds of both sexes. So far, this is a commonplace result.

But a remarkable point comes out in crossing the F_1 birds with pure unpigmented brown Leghorns. The F_1 ♀ × ♂ brown Leghorn gives only unpigmented or practically unpigmented birds. But ♀ brown Leghorn × F_1 ♂ gives a definite proportion, 1 in 8, of pigmented birds; *and these are always* ♀ ♀—again the "Knight's move." The unaffected ♂ can transmit, but only to the opposite sex. The difference in the transmitting power of the two sexes is still more strongly brought out when the ♀ brown Leghorn is mated with a ♂ silky. In such an experiment we found that the ♂ ♂ were practically unpigmented, but that all the ♀ ♀ were pigmented. The case is in reality more complicated than I have here indicated, owing to the occurrence of different grades of pigmentation and for other reasons. Nevertheless we hope soon to put

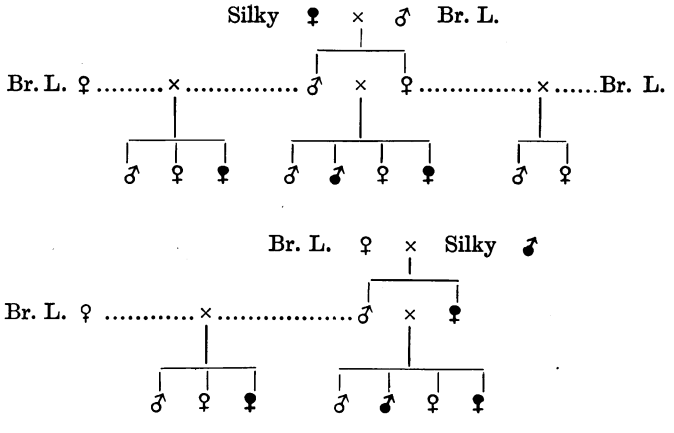


FIG. 13

forward a scheme to cover it. The explanation will probably involve the conception of sex as a character transmitted on Mendelian lines, together with the existence of gametic coupling between the factors influencing pigmentation and the sex factors. More at present we cannot say, but these facts are sufficient to indicate that cases not dissimilar to those of the sex-limited diseases in man occur among animals, and we may reasonably hope that the solution of the problem of the silky fowl will throw further light upon diseases like hæmophilia and peroneal atrophy.

There is little doubt but that a knowledge of Mendel's principles must be of value in the study of disease, for when once Mendelian analysis has established the operation of the law, and the nature of the

characters concerned, we are in a position to predict, always the probable, sometimes the inevitable, result of a given mating. When a brachydactylous man marries a normal woman we are certain that there is an even chance of any given child being born diseased or normal. When two normal people with night-blind parents and grandparents marry we may predict with confidence that none of their children will inherit the disease.

But before the Mendelian nature of a disease can be established, full and accurate pedigrees must be forthcoming. And in the collection of such pedigrees too much emphasis cannot be laid upon the necessity of paying as much attention to the normals as to the affected, for the interpretation turns as largely upon their behaviour as upon that of the diseased.

The pedigree accomplished, the next task is that of reading it. If it is a simple case of dominance and recessiveness this will be an easy matter. If it is more complex the key may possibly be found in some one or other of the standard cases which have been, and are now being worked out in plants and animals; for careful experimental work in animals and plants must for a long time be the basis upon which the student of human heredity will have to build.

But, perhaps, after all, our pedigree may prove refractory, and may refuse to take its place in any known hereditary scheme. In such cases we may be dealing with a disease which is not, in the true sense of the word, hereditary, because not represented in the structure of the gamete, but, like syphilis, is caused by a foreign invasion. It is in the hope of gaining information from those who are so well qualified to speak upon these matters that I would venture to suggest that diseases fall into at least three classes:—

(1) Diseases which depend directly upon a structural change in the gamete, either by the addition or subtraction of some character as compared with the normal, *e.g.*, night-blindness, brachydactyly, alkaptonuria.

(2) Diseases in which such structural change of the gamete is without visible effect, but which renders the individual liable to invasion by bacteria, &c. The disease is not manifested unless the structural change and the external organism are both present; *e.g.*, rust in wheat.

(3) Diseases caused by external invasion, for which immunity, as implied by gametic structure, is not known to exist, *e.g.*, syphilis, ankylostomiasis.

Of these three classes we should expect (1) and (2) to exhibit the phenomenon of Mendelian heredity in some form or another. But class (3) is of an entirely different nature and cannot be inherited in the biologist's sense of the term. It seems not inconceivable that Mendelian analysis may be sometimes valuable as a criterion for separating this class of disease from the others. Undoubted non-Mendelian inheritance may possibly in some cases suggest renewed search for a parasite hitherto overlooked.

In conclusion, may I express the hope that those present to-night will not let slip such opportunities as they may have of collecting evidence upon the transmission of disease? Except in a few cases the available data are scanty, nor are they always of great value owing to a not unnatural tendency to pay less attention to the normals than to the affected. To-day we realise that all are equally important. It is only through complete records that we can hope eventually to disentangle the complexities of inheritance—to determine the unit characters involved, and to state our problems clearly to the chemist, with whom the solution must ultimately rest.

DISCUSSION.

The PRESIDENT (Dr. Newsholme) said that Mr. Punnett's address had been a most valuable and interesting one, as well as the demonstration, opening up a large field for discussion by both physicians and epidemiologists.

Dr. H. M. VERNON (Oxford) sent a communication, which was read by Dr. G. S. Buchanan. The writer regretted his inability to be present and said that medical men should feel greatly indebted to Mr. Punnett for describing to them the recent work on Mendelism, but he hoped that they would not be carried away by the idea that it was the one all-important question of heredity, especially in regard to hereditary disease. All the three diseased conditions quoted by the author of the paper were very rare ones, probably not present in more than 1 per 100,000 of the population, yet those were the best instances he could adduce of the working of the law. Also in regard to normal characters, Dr. Vernon believed that eye-colour alone (and possibly to a slight extent hair-colour) have been shown to conform at all with the law. All the other measurable characters in man and cases of hereditary transmission of disease (as insanity, gout, disposition to tubercle, &c.) had nothing to do with the law, as far as could be seen. The gametes corresponding to such characters were able to blend and form blended zygotes, which gave rise to blended gametes and not segregated alternative ones, as was required by Mendel's law. The vast amount

of work done by Galton, Pearson and others on the transmission of such blended characters and their relation to the characters of the parents, grandparents, &c., was practically ignored by the Mendelians. For the average medical man a knowledge of the laws of ancestral heredity, as defined by the workers mentioned, appeared more important than a knowledge of the segregated transmission of a few very rare diseases, interesting as such cases were.

Dr. A. E. GARROD, referring to the suggestion contained in Mr. Punnett's paper that alkaptonuria might result from the absence of an enzyme which brought about the disintegration of the benzene ring of the aromatic fractions of proteins, said that this view had been suggested in several quarters on quite other grounds than those of heredity, and that from the standpoint of chemical physiology there was much to be said in its favour. He called attention to the difficulty of obtaining satisfactory evidence of the occurrence of such chemical "sports" in the families of the patients. Although alkaptonuria was a fairly evident anomaly it was not easy to find out whether members of back generations of a family had stained their napkins in infancy or had passed urine which darkened on standing. In connection with cystinuria the difficulty was still greater, seeing that many cystinurics did not form calculi or develop any conspicuous urinary troubles. Hence, for such anomalies it was practically impossible to construct family trees showing, with any degree of accuracy, the numbers of normal and abnormal members in successive generations. The bearing of the Mendelian theory upon the question of the effects of consanguineous marriages, to which Mr. Punnett had not referred in his paper, appeared to Dr. Garrod to be of extreme interest. The literature dealing with this subject was most unsatisfactory, and most authors had set out to show that consanguineous marriages had or had not evil consequences for the offspring. On the other hand, the explanation that a rare recessive character was most likely to appear in the offspring of the intermarriages of members of a family who produced the recessive gametes seemed to remove the question beyond the zone of prejudice and to explain in a satisfactory manner why so large a proportion of human recessives, such as albinos and alkaptonurics, were the offspring of marriages of first cousins. It also explained the undoubted connection between such marriages and the appearance, in several children of a family, of an anomaly which had not manifested itself in immediately preceding generations.

Mr. MAJOR GREENWOOD, JUN., said he felt that, as a pupil of Karl Pearson, he ought to say something with regard to the Mendelian school, and support to that inclination was afforded by Dr. Vernon's letter, there being a tendency, apparently, on the part of the Mendelians, to sing a Te Deum on the slightest provocation. Not so much in Mr. Punnett's exposition as in the proof of the paper which had been circulated, there was a long list of the conquests achieved by the Mendelian school, and, in face of that, the adherents of that school had no right to complain if criticism were minute in view of its being asserted to be *the* theory instead of *a* theory of heredity. It was desirable to know what meaning the Mendelians attached to the word "proof." A statistician recently

—perhaps enraged by Mr. Lock's peculiar ideas on the subject of regression—said that approximations could be classified into three groups: close approximations, rough approximations, and Mendelian approximations. But, apart from Mendelian approximations, the experimental side of the question was rather interesting. With regard to moths, to which the author had briefly alluded, Mr. Doncaster, a Mendelian who had worked on that subject, as a result of his own and other people's experiments on several species, concluded that black wing coloration was, in general, a dominant character in the absence of purple, purple being dominant over black in moth breeding (Prout's *Ferrugata*). In studying that subject, Mr. Prout, the leading English authority on Geometrid moths, concluded that the geometers offered, for breeding, a good field in the direction under discussion. There were two very well marked forms of *Acidalia virgularia*—one in the South of France and the other around London, the melanic variety. The non-expert could readily distinguish those two varieties. They were bred for six generations, and were found to breed perfectly true. Prout and Bacot then obtained specimens from the South of France, and crossed them with specimens from Clapton. Seven or eight crossings were made, and they reared the first generation, and from the pairs seven generations had been bred through, about 2,500 moths resulting. Examination showed that there was not a trace of segregation; in each generation there was a blend. That was of very special importance, because Mr. Prout had not taken up moths as a pawn in the game, but as a student of geometers; and one knew that an entomological specialist was a man who was very keen on creating differences where none existed or where none were apparent to other people. If such a man could not distinguish between offspring, it might be concluded that no segregation had taken place. Mendelians might say that was not a simple unit character; but what was to be the criterion of the unit character? If melanism were a simple character in Doncaster's cases but not here, then the definition of a unit character was: a character which was inherited according to Mendel's theory. That had a superficial resemblance to arguing in a circle. Years ago, Professor Karl Pearson published a paper in which he showed that on the scheme propounded by Galton parental regression would be, in general, linear, but on the Mendelian theory, as then propounded, it would take the form of a hyperbola. There were many things about the Mendelian theory which might be hyperbolic, but he doubted whether regression was one of them, and the scheme had been so modified since that he thought one was entitled to ask for a definition of unit character. With regard to night-blindness, in regard to which such a splendid pedigree was exhibited, it was said to be due to the absence of visual purple in all probability. But later it was more than a suggestion and was fitted into the scheme. It would be interesting to hear Mr. Punnett's evidence that absence of visual purple was the cause. He believed it was a deduction from a theory. In 1883, Parinaud and von Kries simultaneously propounded the theory that normal vision depended on a double mechanism; one affecting the cones and fovea, giving ordinary daylight vision, and the other associated with the rods of visual purple, which was characterised by sensitivity

to feeble light, and might be regarded as the twilight factor. They suggested that night-blindness might be a condition in which the visual purple of the rods was either absent or functionless. Everyone would be glad of proof of the statement. The only way of testing it would be to inveigle a subject of night-blindness into a dark room, keep him there two hours, kill him, and then remove the retina and soak it in bile-salts, which, of course, was not done in any of the cases. Messmer[1] examined a small number of cases very carefully, and announced that the night-blinds could be differentiated into cases in which dark adaptation was quite normal when produced, but there was a very long latent period. But the other type had a normal reaction-time after being brought into the dark, but when the adaptation was produced it was very feeble in extent. So that night-blindness was probably not the simple thing which could be represented by black dots in a pedigree chart; it was not simply a question of being night-blind or not night-blind, hornless or horned, but there were gradations. In the night-blinds discussed by Mr. Punnett, Mr. Nettleship admitted he could not examine all the cases, and the conditions did not favour him. So the suggestion was that, at least in regard to night-blindness, there was not enough knowledge to enable it to be dismissed in the simple way suggested by the ingenious Mendelians. It would be better to collect much larger statistics of the various commoner pathological conditions. He need not refer to tuberculosis, which Karl Pearson had recently investigated. Assuming that the tubercular predisposition was a simple recessive character, he showed that the scheme failed utterly, the disproportion between the predicted and the actual in one case being as 57 to 100, which he, Mr. Greenwood, thought was outside even the Mendelian limits of approximation. Therefore, in regard to pathological conditions and inheritance, they had no right to regard these conditions as being so simple as to permit of their being summarised in a simple Mendelian pedigree.

Mr. UDNY YULE said he spoke simply as a statistician who was interested in the question of heredity. He was at one with Mr. Greenwood in being less hopeful than the author as to the wide applicability of the Mendelian principles to state medicine. Two distinct and important points arose out of the paper: first, as to the applicability of the principles; secondly, as to the increased effectiveness of state medicine, granted even that those principles were widely applicable. Many of the cases dealt with by the author referred to the inheritance of abnormalities rather than to disease properly so termed, *e.g.*, such diseases as tuberculosis or insanity. Supposing a definite germinal characteristic decided whether or not a person should have the tubercular diathesis, that did not mean that that man would certainly have tuberculosis, merely that he was liable to have it; he might die of something quite distinct, after living as long as the normal man. And was not that the case in regard to most diseases? The matter was extremely complicated, even if the germinal processes were Mendelian. In reading Karl Pearson's investigation concerning tuberculosis and Heron's on the inheritance of insanity he had not felt satisfied with the

[1] *Zeitschr. f. Phys. und Psych. d. Sinnesorg.*, xlii., p. 83.

arguments as to the non-applicability of Mendelian principles to the germinal processes, so he went into the question himself, and in the end he had not felt convinced whether the Mendelian principles applied or no. If insanity were recessive, all we knew was that a man exhibiting insanity was a pure recessive. But his sane mate was not necessarily a dominant, nor a heterozygote, but might be also a pure recessive who simply had not had time or opportunity to exhibit that character. The case was much more complicated than a first consideration would lead one to suppose. Matings between sane persons might be matings between pure recessives, between recessives and heterozygotes, or between dominants. In what proportion was the various mating likely to occur? One could only form some theory on the assumption of random mating, and that he had tried, but the proportions of insane offspring did not work out very well. Quite obviously their divergences from the observed were outside the limits of probable error. Further, if the mating were really random, one would not get a random selection of such matings between recessives and heterozygotes by taking those matings in which at least one of the offspring was insane, because mating recessives with recessives would give a larger proportion of insane cases amongst the offspring than would the mating of heterozygotes with recessives. After all, what had to be dealt with was the character which was exhibited, and he agreed with the last speaker that in cases like these the actuarial method was likely to yield more valuable information to the medical man than a discussion on the basis of germinal laws, which might hold for the germ-cells but need not hold for the body, seeing how much the element of circumstance entered into the matter. Other factors as important as heredity must be taken into consideration. The actuarial statement included what the germinal statement did not, namely, those factors of disturbance which were of equal importance with the factors of pure heredity. It was necessary to know, for example, in how far selection operated on the different types of character which were subject to heredity; how far there was selection by death; how far by non-marriage, and, if such person did marry, how far there might be selection by fertility or non-fertility in the case of persons possessing one character or another. The importance of such disturbances seemed to be enforced by some of the figures illustrating the Mendelian cases, which puzzled him very much. Assuming that brown or duplex eye-colour was dominant over blue, if matings of persons of different eye-colours were random (and that was very nearly true), it was to be expected that in the population there would be three persons with brown eyes to one with blue; but that was not so. There were more blues than browns. The same applied to the examples of brachydactyly. The author said that brachydactyly was dominant. In the course of time one would then expect, in the absence of counteracting factors, to get three brachydactylous persons to one normal, but that was not so. There must be other disturbing factors of equal importance. Finally, to pass to his second point, he doubted whether the theory would at all largely increase the physician's effectiveness in state medicine. On that point Mr. Punnett seemed to be extraordinarily hopeful. Supposing it were found that a certain diathesis

was subject to Mendelian principles, did one advance much further, either in treating the individual or in taking general measures? Could the physician do more in the light of such knowledge than he could now? Could he do more than endeavour to keep the individual free from infection and from predisposing conditions? It had been suggested by many writers that the characters were amenable to human control by controlling marriage. That, however, seemed to him a chimerical idea, and not in the bounds of the practical at present. Further, in such cases as tuberculosis and insanity, where one could not be certain as to the germinal constitution of the individual, even marriage control would largely break down. He concluded by thanking the author for his paper.

Dr. T. LEWIS said that, in dealing with deformities of the hands and feet, certain cases had been given by the author as instances, which agreed fairly well with the Mendelian theory. But it was important to take account of the fact that there was a tendency for the condition to die out in successive generations. In examining a number of cases of deformities of the hands and feet he had found that to be true. That was the crux of the whole matter in its applicability to disease.

Dr. FREMANTLE asked what was the area over which the author took his human statistics. If it was as small as it appeared to be, the margin of error was far too great. Still-births and, moreover, miscarriages could not possibly have been included. If they were not taken into consideration in drawing conclusions, for instance as to night-blindness, it seemed to him that those conclusions must be thrown out of gear. Secondly, having established full and accurate pedigrees, including still-births and miscarriages, it became necessary to interpret them, and in doing so it was necessary to come back to the original principle: that inheritance of various qualities depended upon the union of the gametes. It was surely only one single spermatozoön out of 50,000 at the very least which was selected by various chances in the process of impregnation to form the offspring; and it was pure chance whether that spermatozoön had the particular characteristic in the dominant or in the recessive. Surely the element of chance was mathematically so enormous, and the characters of any importance so complex, that only an inconceivably large number of offspring could eliminate chance and represent the mathematical bringing together of the gametes which had been represented.

Sir SHIRLEY F. MURPHY thought the Section ought to thank Mr. Punnett very much for his excellent paper, as the subject matter of it was full of interest. Mendel's law seemed to be established for certain characteristics and within certain limits. How far it might go beyond that was a matter for further enquiry and research. One could not imagine conditions under which Mr. Punnett was going to interfere with the ways of love, but the theory had arrived experimentally at the stage of being of considerable importance to the agriculturalist, and even if it did not go beyond that it would have served its purpose. The interest of that Section in the matter was not as to how far it could be applied, but how far the law was one by which Nature worked. He

moved a hearty vote of thanks to Mr. Punnett. This was supported by the President and carried.

Mr. PUNNETT, in replying to Dr. Garrod, said it was possible for a diseased (or anomalous) individual to come from two normal parents even though the diseased condition behaved as a dominant to the normal. Among poultry colour was in certain cases dominant to white, yet, when two pure white strains, each recessive to colour, were crossed only coloured birds resulted. Two things were necessary for the production of colour in this case, and absence of either resulted in a white bird. Such experiments suggested that many of the enzymes might be of a double nature, and he believed that this had already been shown for the action of diastase on starch and for the lipolytic action of the liver-cells. The case of the moth, cited by Mr. Greenwood, was a very rare one, and interesting on that account. Mr. Bateson had come across another such case in a butterfly (*Pararge egeria*). Much more experimental work was required upon the heredity of these forms, and until it was forthcoming it was safer to suspend judgment. Dr. Greenwood had asked for a definition of a unit character. He would to-day define a unit character as one which exhibited Mendelian heredity. It was a crude definition, but it could be tested by facts, and facts, after all, were the basis upon which the Mendelians were building. With regard to the absence of visual purple in night-blind people, he was quoting a view which he understood was generally received among those most qualified to judge. He quite agreed with Mr. Greenwood that the experimental method was the only way of settling this, as well as many other questions connected with heredity. But whatever the cause or causes it made no difference to the facts of transmission of night-blindness. Mr. Greenwood's argument that the inheritance of tuberculosis was non-Mendelian depended on the assumption that the tubercular predisposition was a simple recessive character. He wondered what medical men would say to that, for he had always understood that the etiology of the disease was by no means simple. He was certain that no Mendelian would have the temerity to-day to make the assumption upon which Mr. Greenwood's argument was based. Mr. Yule wondered why the nation was not slowly becoming brown-eyed and brachydactylous, since these characters were both dominant. So it might be for all he knew, but this made no difference to the mode of transmission of eye-colour or brachydactyly. In regarding the breeding of man as mixed up with all manner of conventions and prejudices he quite agreed with Mr. Yule, but these were matters concerning ethics rather than heredity. Dr. Lewis suggested that the brachydactylous condition tended to die out in successive generations, presumably as the result of crossing with the normals. He could not agree with this optimistic view. A glance at Dr. Drinkwater's table, for instance, showed that in the last generation the children of brachydactylous people were relatively just as numerous as ever, and were almost exactly the expected 50 per cent. of the total. Dr. Vernon's letter raised the old controversy between the Mendelians and the biometricians, and dwelt upon the practical value of the law of ancestral

heredity as defined by Pearson and others. But it did not seem to him that a law which utterly collapsed before such simple facts as the production of colour from two pure strains of poultry or sweet peas was likely to be of much value to the average medical man or to anybody else. Mendelian inheritance has now been demonstrated for numbers of most diverse characters in plants and animals. It has also been shown to hold for a few simple cases in man where the evidence has been collected carefully and critically. How far it applies must be a matter of opinion until much more in the way of accurately recorded pedigrees is forthcoming. Facts alone can decide the matter, and if this paper did a little to stimulating the collection of such facts it would have amply repaid whatever pains went to the making of it.